OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

Ottawa Hull K1A 0C9

(21) (A1) 2,136,288
(22) 1994/11/21
(43) 1995/05/24

(51) Int.Cl.[5] C07D 487/04; C07D 519/00; A61K 31/495; A61K 31/535

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Imidazopyridazines

(72) Dorsch, Dieter - Germany (Federal Republic of) ;
Mederski, Werner - Germany (Federal Republic of) ;
Osswald, Mathias - Germany (Federal Republic of) ;
Schelling, Pierre - Germany (Federal Republic of) ;
Beier, Norbert - Germany (Federal Republic of) ;
Lues, Ingeborg - Germany (Federal Republic of) ;
Minck, Klaus-Otto - Germany (Federal Republic of) ;

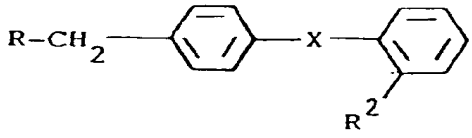
(71) Merck Patent Gesellschaft mit beschränkter Haftung - Germany (Federal Republic of) ;

(30) (DE) P 43 39 868.5 1993/11/23

(57) 8 Claims

Abstract of the Disclosure

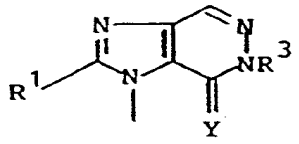
Novel imidazopyridazine derivatives of formula I



I

wherein

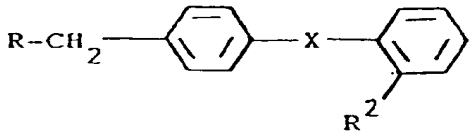
R is



and R^1, R^2, R^3, X and Y are as defined in Patent Claim 1, and their salts, exhibit antagonistic properties towards angiotensin II and can be used for the treatment of hypertension, aldosteronism, cardiac insufficiency and increased intraocular pressure, and of disorders of the central nervous system.

Patent Claims

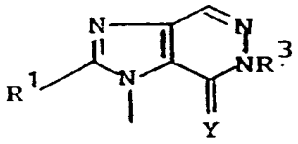
1. Imidazopyridazine derivatives of formula I:



I

wherein

R is



R^1 is A, alkenyl or alkynyl each having up to 6 C atoms, C_3-C_7-cycloalkyl-C_kH_{2k}- or C_1-C_6-alkyl, wherein a CH_2 group is replaced by O or S,

R^2 is H, COOH, COOA, CN, NO_2, NH_2, NH-COR^4, NH-SO_2R^4 or 1H- tetrazol-5-yl,

R^3 is a C_1-C_{10}-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl group which is mono- to tetrasubstituted by C_3-C_8-cycloalkyl, CN,COOH, COOA, Ar, Het^1, Het^2, -CO-R^5, -CO-Ar, -CO-Het^2, -CO-NR^6R^7, -CO-R^8, -C(=NR^9)-A), -C(=NR^9)-Het^2, NO_2, NR^6R^7, -NR^{11}-COR^5, -NR^{11}-COAr, -NR^{11}-COOA, -NR^{11}-SO_2R^5, -NR^{11}-SO_2Ar, OR^{10}, -S(O)$_m$-A, -S-(O)$_m$-Ar, -SO_2-NH-Het^2, -SO_2-OR^{11}, Hal and/or 1H-tetrazol-5-yl and in which a CH_2 group can also be replaced by an O or S atom; or unsubstituted C_2-C_6-alkenyl or C_2-C_6-alkynyl,

R^4 and R^5 are each C_1-C_5-alkyl, in which one or more H atoms can also be replaced by F,

R^6 and R^7 are each H, A, C_2-C_6-alkenyl or C_2-C_6-alkynyl, Ar, ArC_nH_{2n}- or Het^2,

R^6 is also -CH_2COOA, -SO_2-A or -SO_2-Ar,

R^6 and R^7 together are also an alkylene chain having 2-5 C atoms, which can be monosubstituted or polysubstituted by carbonyl oxygen, Ar, Het^2, -CO-Ar, -COOA,

$-CO-N(A)_2$, $-CH_2OH$, $-SO_2-Ar$ and/or -NH-CO-A and/or interrupted by O or by $-NR^{12}-$,

R^8 is $-NH-CHR^{11}-COOH$, $-NH-CHR^{11}-OOA$, $-CH_2S(O)_m-Ar$, $-CH_2C-COOA$, $-C_nH_{2n}-NO_2$, $-C_nH_{2n}-NR^6R^7$ or $-C_nH_{2n}-NH-COOA$,

R^9 is H, OH, CN, R^{13}, OR^{13} or OAr,

R^{10} is H, C_1-C_{10}-alkyl which can be substituted by Ar, Het^2, COA or COAr, or is Ar, COA, COAr or $CONR^6R^7$,

R^{11} is H or A,

R^{12} is H, A, Ar, COOA, Het^2 or SO_2Ar,

R^{13} is A, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

X is absent or is -NH-CO-, -CO-NH-, -O-CH(COOH)-, -NH-CH(COOH)-, -NA-CH(COOH)-, -CH=C(COOH)-, -CH=C(CN)- or -CH=C(1H-tetrazol-5-yl)-,

Y is O or S,

A is C_1-C_6-alkyl,

Ar is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R^5, OR^5, COOH, COOA, CN, NO_2, NH_2, NHA, $N(A)_2$, $NR^{11}-COR^5$, $NR^{11}-COAr^1$, $NR^{11}-SO_2R^5$, $NR^{11}-SO_2Ar^1$, Hal or 1H-tetrazol-5-yl,

Ar^1 is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R^5, OR^5, COOA or Hal,

Het^1 is a five- or six-membered saturated heterocyclic radical having 1 to 3 N, O and/or S atoms, which can be monosubstituted by carbonyl oxygen or $=NR^9$ and/or whose ring N atom(s) can in each case be substituted by A or Ar,

Het^2 is a five- or six-membered heteroaromatic radical having 1 to 3 N, O and/or S atoms, which can also be fused with a benzene or pyridine ring and/or monosubstituted or disubstituted by A,

Hal is F, Cl, Br or I,

k is 0, 1, 2, 3 or 4

m is 0, 1 or 2 and

n is 1, 2, 3, 4, 5 or 6,

and their salts.

2. a) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-benzyl-7-oxo-1H-imidazo[4,5-

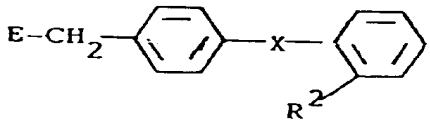
d]pyridazine and its potassium salt;

b) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-α-isopropoxycarbonylbenzyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt;

c) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-N,N-dimethylcarbamoylmethyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt.

3. Process for the preparation of imidazopyridazines of formula I according to Claim 1, and their salts, characterized in that

(a) a compound of formula II:



II

wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and

R^2 is as defined in Claim 1,

is reacted with a compound of formula III:

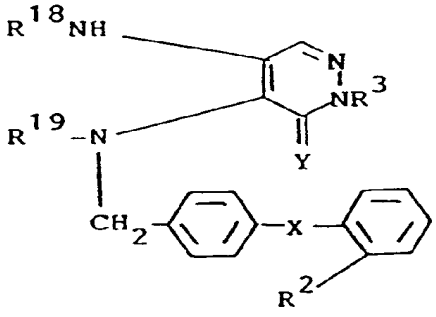
H-R III

wherein

R is as defined in Claim 1,

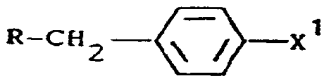
or

(b) a compound of formula IV:



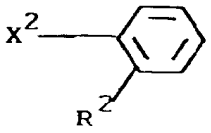
IV

wherein
R^{14} is R^1-CO or H,
$R^{15}$is H (if R^{14} is R^1-CO) or R^1-CO (if R^{14} is H), and
R^1, R^2, R^3, X and Y are as defined in Claim 1,
is treated with a cyclizing agent,
or
(c) to prepare a compound of formula I wherein X is -NH-CO- or -CO-NH-, a compound of formula V:



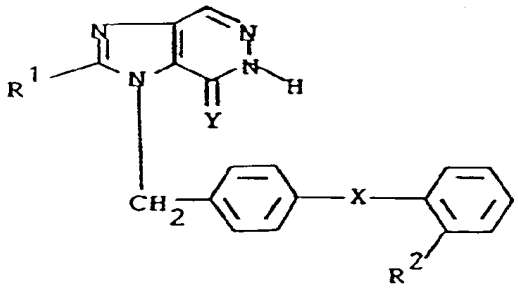
V

wherein
X^1 is NH_2 or COOH, and
R is as defined in Claim 1,
or a reactive derivative of this compound, is reacted with a compound of formula VI:



VI

wherein
X^2 is COOH (if X^1 is NH_2) or NH_2 (if X^1 is COOH), and
R^2 is as defined in Claim 1,
or with a reactive derivative of this compound,
or
(d) a compound of formula VII:



VII

wherein

R^1, R^2, X and Y are as defined in Claim 1, is reacted with a compound of formula VIII:

$$E\text{-}R^3 \qquad \text{VIII}$$

wherein

R^3 and E are as defined above,

or a reactive derivative of such a compound,

or

(e) to prepare a compound of the formula I which contains a $-C(=NR^9)-$ group, a corresponding carbonyl compound is treated with a compound of the formula $H_2N\text{-}R^9$, wherein R^9 is as defined in Claim 1, or

(f) a compound of formula I is freed from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent,

and/or in that one or more radicals R and/or R^2 in a compound of formula I are converted to one or more different radicals R and/or R^2, and/or a base or acid of formula I is converted to one of its salts.

4. Process for the preparation of pharmaceutical formulations, characterized in that a compound of formula I according to Claim 1, and/or one of its physiologically acceptable salts, are incorporated into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or adjunct.

5. Pharmaceutical formulation, characterized in that it contains at least one compound of formula I according to Claim 1, and/or one of its physiologically acceptable salts.

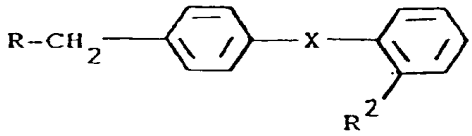
6. Compound of formula I according to Claim 1, and its physiologically acceptable salts, for the control of diseases.

7. Use of compounds of formula I according to Claim 1, and/or their physiologically acceptable salts, for the preparation of a drug.

8. Use of compounds of formula I according to Claim 1, and/or their physiologically acceptable salts, in the control of diseases.

Patent Claims

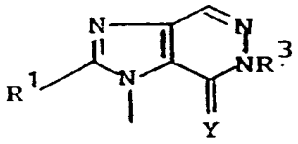
1. Imidazopyridazine derivatives of formula I:



I

wherein

R is



R^1 is A, alkenyl or alkynyl each having up to 6 C atoms, C_3-C_7-cycloalkyl-C_kH_{2k}- or C_1-C_6-alkyl, wherein a CH_2 group is replaced by O or S,

R^2 is H, COOH, COOA, CN, NO_2, NH_2, NH-COR^4, NH-SO_2R^4 or 1H- tetrazol-5-yl,

R^3 is a C_1-C_{10}-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl group which is mono- to tetrasubstituted by C_3-C_8-cycloalkyl, CN,COOH, COOA, Ar, Het^1, Het^2, -CO-R^5, -CO-Ar, -CO-Het^2, -CO-NR^6R^7, -CO-R^8, -C(=NR^9)-A), -C(=NR^9)-Het^2, NO_2, NR^6R^7, -NR^{11}-COR^5, -NR^{11}-COAr, -NR^{11}-COOA, -NR^{11}-SO_2R^5, -NR^{11}-SO_2Ar, OR^{10}, -S(O)$_m$-A, -S-(O)$_m$-Ar, -SO_2-NH-Het^2, -SO_2-OR^{11}, Hal and/or 1H-tetrazol-5-yl and in which a CH_2 group can also be replaced by an O or S atom; or unsubstituted C_2-C_6-alkenyl or C_2-C_6-alkynyl,

R^4 and R^5 are each C_1-C_5-alkyl, in which one or more H atoms can also be replaced by F,

R^6 and R^7 are each H, A, C_2-C_6-alkenyl or C_2-C_6-alkynyl, Ar, ArC_nH_{2n}- or Het^2,

R^6 is also -CH_2COOA, -SO_2-A or -SO_2-Ar,

R^6 and R^7 together are also an alkylene chain having 2-5 C atoms, which can be monosubstituted or polysubstituted by carbonyl oxygen, Ar, Het^2, -CO-Ar, -COOA,

$-CO-N(A)_2$, $-CH_2OH$, $-SO_2-Ar$ and/or -NH-CO-A and/or interrupted by O or by $-NR^{12}-$,

R^8 is $-NH-CHR^{11}-COOH$, $-NH-CHR^{11}-OOA$, $-CH_2S(O)_m-Ar$, $-CH_2C-COOA$, $-C_nH_{2n}-NO_2$, $-C_nH_{2n}-NR^6R^7$ or $-C_nH_{2n}-NH-COOA$,

R^9 is H, OH, CN, R^{13}, OR^{13} or OAr,

R^{10} is H, C_1-C_{10}-alkyl which can be substituted by Ar, Het^2, COA or COAr, or is Ar, COA, COAr or $CONR^6R^7$,

R^{11} is H or A,

R^{12} is H, A, Ar, COOA, Het^2 or SO_2Ar,

R^{13} is A, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

X is absent or is -NH-CO-, -CO-NH-, -O-CH(COOH)-, -NH-CH(COOH)-, -NA-CH(COOH)-, -CH=C(COOH)-, -CH=C(CN)- or -CH=C(1H-tetrazol-5-yl)-,

Y is O or S,

A is C_1-C_6-alkyl,

Ar is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R^5, OR^5, COOH, COOA, CN, NO_2, NH_2, NHA, $N(A)_2$, $NR^{11}-COR^5$, $NR^{11}-COAr^1$, $NR^{11}-SO_2R^5$, $NR^{11}-SO_2Ar^1$, Hal or 1H-tetrazol-5-yl,

Ar^1 is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R^5, OR^5, COOA or Hal,

Het^1 is a five- or six-membered saturated heterocyclic radical having 1 to 3 N, O and/or S atoms, which can be monosubstituted by carbonyl oxygen or $=NR^9$ and/or whose ring N atom(s) can in each case be substituted by A or Ar,

Het^2 is a five- or six-membered heteroaromatic radical having 1 to 3 N, O and/or S atoms, which can also be fused with a benzene or pyridine ring and/or monosubstituted or disubstituted by A,

Hal is F, Cl, Br or I,

k is 0, 1, 2, 3 or 4

m is 0, 1 or 2 and

n is 1, 2, 3, 4, 5 or 6,

and their salts.

2. a) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-benzyl-7-oxo-1H-imidazo[4,5-

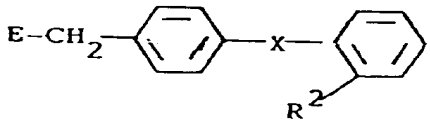
d]pyridazine and its potassium salt;

b) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-α-isopropoxycarbonylbenzyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt;

c) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-N,N-dimethylcarbamoylmethyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt.

3. Process for the preparation of imidazopyridazines of formula I according to Claim 1, and their salts, characterized in that

(a) a compound of formula II:



II

wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and

R^2 is as defined in Claim 1,

is reacted with a compound of formula III:

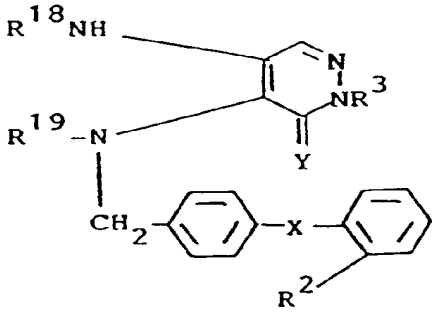
H-R III

wherein

R is as defined in Claim 1,

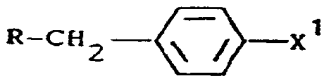
or

(b) a compound of formula IV:



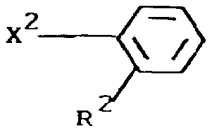
IV

wherein
R^{14} is R^1-CO or H,
$R^{15}$is H (if R^{14} is R^1-CO) or R^1-CO (if R^{14} is H), and
R^1, R^2, R^3, X and Y are as defined in Claim 1,
is treated with a cyclizing agent,
or
(c) to prepare a compound of formula I wherein X is -NH-CO- or -CO-NH-, a compound of formula V:



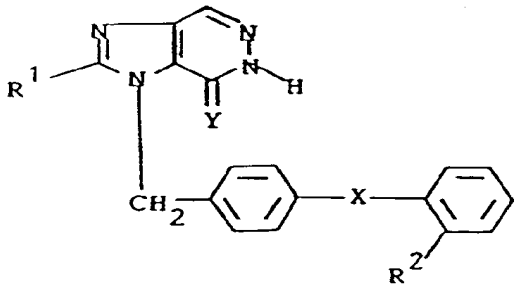
V

wherein
X^1 is NH_2 or COOH, and
R is as defined in Claim 1,
or a reactive derivative of this compound, is reacted with a compound of formula VI:



VI

wherein
X^2 is COOH (if X^1 is NH_2) or NH_2 (if X^1 is COOH), and
R^2 is as defined in Claim 1,
or with a reactive derivative of this compound,
or
(d) a compound of formula VII:



VII

wherein

R^1, R^2, X and Y are as defined in Claim 1, is reacted with a compound of formula VIII:

$$E\text{-}R^3 \qquad \text{VIII}$$

wherein

R^3 and E are as defined above,

or a reactive derivative of such a compound,

or

(e) to prepare a compound of the formula I which contains a $-C(=NR^9)-$ group, a corresponding carbonyl compound is treated with a compound of the formula $H_2N\text{-}R^9$, wherein R^9 is as defined in Claim 1, or

(f) a compound of formula I is freed from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent,

and/or in that one or more radicals R and/or R^2 in a compound of formula I are converted to one or more different radicals R and/or R^2, and/or a base or acid of formula I is converted to one of its salts.

4. Process for the preparation of pharmaceutical formulations, characterized in that a compound of formula I according to Claim 1, and/or one of its physiologically acceptable salts, are incorporated into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or adjunct.

5. Pharmaceutical formulation, characterized in that it contains at least one compound of formula I according to Claim 1, and/or one of its physiologically acceptable salts.

6. Compound of formula I according to Claim 1, and its physiologically acceptable salts, for the control of diseases.

7. Use of compounds of formula I according to Claim 1, and/or their physiologically acceptable salts, for the preparation of a drug.

8. Use of compounds of formula I according to Claim 1, and/or their physiologically acceptable salts, in the control of diseases.